

**Centers for Disease Control and Prevention's Responses to Questions for the Record
From House Committee on Energy and Commerce**

The Honorable Joe Barton and the Honorable John Shimkus

1. From what I know of the CDC/Blount study, your findings were much different than what was found in previous animal studies used by EPA and human data evaluated by NAS. In the conclusion of your study -- as well as in your testimony -- you claim that subsequent, confirmatory analysis is necessary to verify the findings of your study. What things do you believe need to be followed up on? Have you begun this process? How long do you expect this process to take? Can you be absolutely certain that further information gaps will not emerge when you conduct these studies?

Response:

The Blount study is the only study to focus on women with lower iodine levels (women with urine iodine levels less than 100 micrograms per liter). Thus, for this group, there were no previous results with which to compare the Blount results. NAS did not have any data to examine for this group of women, who account for about 36% of women in the U.S. population. Additionally, the Blount study has a very large sample size compared to previous work. The Blount results for men did not show an association between perchlorate levels and thyroid hormone levels. This finding for men was consistent with findings of other studies. For women with iodine levels greater than 100 micrograms per liter, perchlorate levels were associated with thyroid stimulating hormone (TSH) but not total thyroxine.

The Blount publication stated that "Further research is recommended to affirm these findings." We do not think confirmatory analysis is necessary to validate Blount's analysis of the NHANES data. Although we understand that conclusions of causality can rarely be drawn based upon a single study, when viewed within the context of the available clinical literature, the findings of the Blount study are consistent with causality. That is, we think that there is sufficient evidence from clinical studies that perchlorate directly causes decreases in thyroxine at high levels. The remaining scientific question is whether the direct effect extends to the levels of perchlorate found in the U.S. population. For that reason, we do think that another enhanced NHANES analysis of the relationship between perchlorate exposure and thyroid hormone levels in additional women and men should afford additional evidence regarding the strength of the association by providing more than twice the number of women and men to analyze, substantially improving statistical power.

This would help in the following analyses:

- 1) Examination of people who have increased exposure to other environmental factors that could affect thyroid hormone levels. For example, people who have higher thiocyanate exposure (from smoking or dietary sources) are important to examine further for a potential synergistic effect with perchlorate. Smoking, thiocyanate and nitrate were adjusted for in the Blount multiple regression analysis, and increasing the sample size will afford a greater ability to detect potential synergistic effects of these factors with perchlorate. It may also be useful

- to examine differences in dietary intake in more detail.
- 2) Separate analysis for women of childbearing age which is important because of the vulnerability of the fetus.
 - 3) Examination of factors that may account for differences in the observed associations between men and women.

In addition, we plan to examine the relationship of free thyroxine and thyroid autoantibodies to perchlorate levels to supplement and aid in understanding the results of the Blount study on total thyroxine and thyroid stimulating hormone.

A second NHANES study is in the planning stage currently. This study will examine about 50% more men and women than the first study. We hope to be able to combine data from the two studies resulting in about 2.5 times the study sample size we currently have. We cannot with confidence provide a firm finish date for the second study, but a reasonable estimate would be December 2008 to February 2009. We are confident that this additional study will provide more information about relationships between perchlorate exposure and thyroid effects at low population levels.

2. Some witnesses claim that your study is definitive and that further study of this issue is not required. Yet, your study was unique in that the results that you observed were unexpected and different from everything else that previous studies have found. Do you believe it is a good scientific principle to do more study if the results from an existing study are new?

Response

The Blount study is the only study to focus on women with lower iodine levels (women with urine iodine levels less than 100 micrograms per liter). Thus, for this group, there were no previous results with which to compare these results. In addition, a notable strength of the Blount study was its very large sample size (1,111 women) compared to previous work, affording more statistical power to detect potential effects than other studies.

The decision to conduct additional research is a case-by-case decision that is based on a number of factors including the significance of the original findings, the strength and statistical power of previous studies, study design methods and their limitations, and the likelihood that new research will advance scientific understanding. In the current case, we believe there is value in additional study, and we have itemized that value in answer to question 1.

3. You said in your testimony that the CDC/Blount study showed an "association" between urinary perchlorate and increased TSH and decreased total T4 in women 12 and older, who had urine iodine levels < 100 µg/L. It is possible people might assume then that perchlorate actually "caused" the thyroid changes. Was the CDC/Blount study designed to evaluate whether there is a causal relationship between low levels of perchlorate exposure and thyroid function? Can you please clarify the difference between "an association" and "causation?"

Response:

We begin by clarifying the difference between “an association” (referring to a pattern in the data) and “causation” (referring to necessary antecedents to a health outcome). Observational data play an important role in establishing statistically significant associations, evaluating dose response gradients, evaluating the influence of potentially confounding variables, and providing information on coherency and consistency of findings. Causality is difficult to determine and relies on the best scientific assessment of the overall weight of evidence based on multiple important factors. We discuss these factors below. Causality is rarely determined on the basis of a single study, but by the weight of evidence from more than one study.

We find important parallels with the discussion of characterizing causation presented in the recent (2004) Surgeon General’s Report on Smoking. That report concludes that inferences, whether about causality or statistical associations, are always uncertain to a degree, thus the goal (of that report) is to explain and communicate scientific judgments.

The design of the Blount study itself, referred to as cross sectional study, allows assessment of association, dose response gradient and some other factors useful in a weight-of-evidence evaluation. The Blount study, by itself, does not establish causation, but its findings are consistent with causation. Below, we discuss our assessment of the body of literature and the role that the Blount study plays.

The Blount study used NHANES data to examine the potential relationship between perchlorate levels and thyroid hormone levels in men and women. Establishing a causal relationship rests on weight of evidence of a 1) statistically significant association that is independent of other known variables that affect thyroid hormone levels, 2) a logical temporal association (i.e., exposure precedes effect), 3) biological plausibility and 4) coherency, specificity, and consistency of findings (including dose response effects). The Blount study provides information on the statistically significant association with variables available for analysis from NHANES data, and coherency and consistency of findings, but does not address a logical temporal association or biologic plausibility. Previous medical use of perchlorate has demonstrated that use of perchlorate as a drug directly causes decreases in levels of thyroxine. This direct causal effect is at a dose much higher than experienced by the general population and the Blount study is aimed at determining whether this effect extends to these lower perchlorate exposure levels.

The Blount study concluded that for women, there were statistically significant associations between perchlorate levels and total thyroxine and TSH that are coherent in direction and independent of other variables known to affect thyroid function. The “statistically significant association” found between perchlorate levels and total thyroxine levels means that, after adjusting for effects of other NHANES variables known to affect thyroid function (but not all variables which may impact thyroid function, e.g. some dietary factors), perchlorate levels independently predicted thyroid hormone levels, and this independent relationship was unlikely to be explained by chance.

After finding a statistically significant association that is independent of available variables known to affect thyroid function, the justification for a causal relationship relies mainly on other established evidence such as temporality, biological plausibility, and coherency and consistency of findings. Temporality requires that exposure takes place prior to the effect, in this case a change in thyroid hormone. The Blount study is cross-sectional, so it measured perchlorate levels and thyroid hormones at the same time and cannot determine if exposure occurred prior to effect. As noted above, concerning biological plausibility, it is known that high doses of perchlorate inhibit the production of thyroxine, leading to lower total thyroxine levels and higher TSH levels. It is important to note that these exposures were far above those experienced by the NHANES cohort analyzed by Blount et al. Concerning coherency and consistency of findings, after adjustment for other variables known to affect thyroid function, increasing perchlorate levels were found in separate analyses to be associated with both decreasing total thyroxine levels *and* increasing TSH levels. This finding is cited in the paper as coherent in direction. By contrast, if increasing perchlorate had been associated with decreasing thyroxine and *decreasing* TSH, such a finding would not be coherent in terms of an effect on thyroid hormones.

Also relevant to coherency and consistency was the finding that women with lower levels of iodine (urine iodine levels of less than 100 micrograms per liter) had a statistically significant and more pronounced association of perchlorate with thyroid hormone levels. This finding is consistent with the mechanism of perchlorate inhibition of iodine uptake.

4. Did the CDC/Blount study show other known thyroid iodine uptake inhibiting agents as not having any effect or actually in one case showing a reverse effect from the recognized biological normal ranges? How can this be explained?

Response:

In the regression analysis examining TSH levels in women with urinary iodine levels greater than or equal to 100 micrograms per liter, urinary levels of thiocyanate were negatively associated with TSH levels in the final regression model. (Note: This is *not* the group of women with lower iodine levels in whom the statistically significant and more pronounced association of perchlorate and thyroid hormone levels was found). As stated in the paper, a physiologic explanation for the sign of this coefficient for this group of women with higher iodine levels is unclear. The expected effect of thiocyanate on TSH would be for TSH to increase as thiocyanate increases because thiocyanate inhibits uptake of iodine into the thyroid. One possibility for the current finding is that smoking sources of thiocyanate may include exposures to other chemicals that have mixed effects on thyroid function.

5. In the CDC/Blount study, were fluctuations in thyroid hormones among women with low iodine outside normal ranges?

Response:

Most of the women in the Blount study were within the normal range. Many women with levels of thyroid hormones outside the normal range were excluded from analysis because these women were taking thyroid medications or had a known history of thyroid disease. Women taking thyroid medications had to be excluded because the thyroxine measurement would have been measuring the thyroxine they were taking for treatment.

Of the 1,111 women in the final regression analysis in the Blount study, 51 or 4.6% had levels outside the normal range. Of the 356 women with lower iodine levels who were in the final regression analysis, 11 or 3.1% had levels outside the normal range.

Thyroid hormone levels were measured at one point in time, so it was not possible to detect fluctuations in levels of an individual.

6. Do you believe that the CDC/Blount's thyroid study is sufficiently definitive for EPA Headquarters to rely on in moving forward with a regulatory determination on perchlorate as well as use by EPA Regions in developing site-specific risk assessments and cleanups?

Response:

As we state in CDC (2004), there are differences between both the process and goals of causal inference and decision making. We believe it is more appropriate for EPA to make this determination, based on its own scientific expertise and experience administering the specific statutes at issue.

7. In commenting on the CDC/Blount study, which you spoke of in your testimony, the American Thyroid Association (ATA) states that "[t]hese findings are intriguing, although several features of the study may limit the immediate application to guidelines for perchlorate exposure standards." The ATA also states that "further laboratory information is necessary before the implications of the findings can be understood." The Blount study itself says "further research is recommended to affirm these findings." Would you agree with the ATA and the Blount study in this regard, specifically that more study is needed and this study alone is not sufficient for setting a regulatory standard, and could you please explain your answer?

Response:

Concerning regulation, as noted above, we defer to EPA on what is sufficient for setting an EPA regulatory standard.

The Blount publication stated "Further research is recommended to affirm these findings." Another enhanced NHANES analysis of the relationship between perchlorate exposure and thyroid hormone levels in additional women and men should provide more than twice the number of women and men to analyze, substantially improving statistical power.

This enhanced statistical power would help in the following analyses:

- 1) Examination of people who have increased exposure to other environmental factors that could affect thyroid hormone levels. For example, people who have higher thiocyanate exposure (from smoking or dietary sources) are important to examine further for a potential synergistic effect with perchlorate. Smoking, thiocyanate and nitrate were adjusted for in the Blount multiple regression analysis, and increasing the sample size will afford a greater ability to detect potential synergistic effects of these factors with perchlorate. It may also be useful to examine differences in dietary intake in more detail.
- 2) Separate analysis for women of childbearing age which is important because of the vulnerability of the fetus.
- 3) Examination of factors that may account for differences in the observed associations between men and women.

In addition, we plan to examine the relationship of free thyroxine and thyroid autoantibodies to perchlorate levels to supplement and aid in understanding the findings of the Blount study on total thyroxine and thyroid stimulating hormone. The ATA also suggested adding free thyroxine to the measurements in the Blount study.

8. Many of your studies look at the health effects of various things on people of differing socio-economic backgrounds. Did your recent perchlorate study extrapolate that information?

Response:

In the Blount study, race/ethnicity was a variable included in the regression models, but it was not a significant predictor of thyroid hormones. We did not examine a variable that tracked income.

9. Do you agree with Dr. Utiger that people with hypothyroidism should compensate for potential perchlorate exposures through greater dietary intake of iodine rich foods and vitamins?

Response:

We believe that people with hypothyroidism should be under the care of a physician for appropriate diagnosis and treatment. Adequate intake of iodine has previously been recognized as important for healthy thyroid function. The Blount study results would reinforce that recommendation for women.

The Honorable Albert Wynn

1. Are calculations for median estimated dose of perchlorate for adults about 1/10 of EPA's reference dose of 24.5 ppb.?

Response:

Yes; for adults, the median estimated dose (0.064 µg/kg day) is about 1/10th of the EPA reference dose (RfD) (0.7 µg/kg day).

2. Is it true that the 2006 NHANES study found measurable amount of perchlorate in all 2,820 survey participants and that the levels of perchlorate found in children were 65 percent higher than those found in adults?

Response:

Yes, all 2820 study participants had measurable perchlorate in urine, with the creatinine-adjusted perchlorate levels in children (6-11 years old) being 65% higher than the creatinine-adjusted perchlorate levels in adults (aged 20 years and older).

3. The CDC 2006 NHANES study was peer reviewed and tested multiple times and CDC testified that it has a high level of confidence in its findings. Does CDC agree that this study is based on the best available, high quality, peer reviewed science and that the data was collected by accepted methods?

Response: Yes

4. CDC's second study examined the relationship between urine perchlorate levels and thyroid hormone level, 12 years old and up using perchlorate levels common in the US populations that are much lower than those used therapeutically. This study was also peer reviewed. Is CDC planning a second study to affirm these findings and expand on the study?

Response:

Yes. A second study is in the planning stages and will include at least as many men and women as the first study.

5. Is it true that CDC NHANES was peer reviewed and is in compliance with the information Quality Act, Pub. L. NO. 106-544?

Response:

The CDC National Health and Nutrition Examination Survey (NHANES) is in compliance with the Information Quality Act. NHANES is conducted by CDC's National Center for Health Statistics (NCHS). Statistical information is subject to quality guidelines requiring federal agencies to adopt a basic standard of quality (including objectivity, utility, and integrity) and to incorporate quality criteria into agency information dissemination practices, issued by the Office of Management and Budget (OMB). Information dissemination practices of CDC's NCHS, including information dissemination associated with NHANES, comply with these OMB guidelines. In addition, the NHANES undergoes extensive review both within the Department and by OMB as a way to ensure the integrity of the data. NCHS is committed to integrating the

principle of information quality into every phase of information development, including creation, collection, maintenance, and dissemination. Detailed information about how NCHS assures the quality of information disseminated to the public is available on the NCHS Web site <http://www.cdc.gov/nchs/about/quality.htm>. The Information Quality Bulletin for Peer Review issued by OMB enhances the practice of peer review of government science documents. As specified in the Federal Register Notice on this policy (Vol. 70, No. 10, Page 2677), the Bulletin provides an exemption to the peer review requirement for, "Routine statistical information released by federal statistical agencies (e.g., periodic demographic and economic statistics) and analyses of these data to compute standard indicators and trends (e.g., unemployment and poverty rates)." As recommended by the Interagency Council on Statistical Policy, OMB considers NHANES to be covered by this exemption.

In the case of the 2006 analysis of the perchlorate data that is the subject of this question, scientists in the National Center for Environmental Health of the CDC analyzed the data and wrote the two publications with the standard disclaimer on the publications that the findings and conclusions in this report are those of the authors and do not necessarily represent the views of CDC. These publications were peer-reviewed by outside experts before being submitted for publication and also peer-reviewed by reviewers of the publishing journals.

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6. Various studies have shown that nursing and bottled fed infants could receive doses of perchlorate from breast milk above EPA's RfD of 24 ug/L. Recent studies have determined the existence of perchlorate doses that were above EPA's RfD of 24 ug/L for infants drinking reconstituted formula made with water containing perchlorate (Baier-Anderson et al. 2006)(Kirk et al. 2005) and have also estimated that nursing infants could receive doses above the RfD even without considering the added exposure associated with EPA's preliminary remedial goal of 24 ug/L (Pearce et al. 2007 and Kirk et al. 2007). Please describe whether the Agency is considering the impact of perchlorate on nursing and bottle-fed infants and/or whether the Agency intends to utilize the above referenced studies or conduct its own studies on the impact of perchlorate on nursing and bottle-fed infants.

Response:

We are actively investigating perchlorate exposure and thyroid function in both breast-fed and bottle-fed infants. We first developed high-quality analytical methods for measuring perchlorate in the following body fluids that are relevant to a baby's exposure: breast milk, amniotic fluid, cord blood, newborn dried blood spots, and newborn urine. Our ongoing collaborative studies of perchlorate exposure in infants are listed below:

- Perchlorate exposure and thyroid function in breast-fed and formula-fed infants. In collaboration with Dr. Water Rogan (National Institute of Environmental Health Sciences), we are assessing perchlorate exposure and thyroid function in infants (ages 1 – 12 months) who are consuming either breast milk or infant formula.

- Perchlorate exposure in lactating women and breast-fed infants in West Texas. In collaboration with Dr. Purnendu Dasgupta (University of Texas, Arlington), we are assessing perchlorate exposure in lactating mothers and their breast-fed infants. Perchlorate exposure may be higher in West Texas compared with the rest of the country because of prevalent consumption of well water with naturally-occurring perchlorate contamination.
- Characterizing perchlorate exposure in the developing fetus. In collaboration with Dr. Mark Robson (Rutgers University), we are measuring perchlorate in maternal urine, maternal serum, amniotic fluid, and cord blood. By measuring perchlorate levels in different fluids from the mother and the infant, we can better understand how a mother's exposure to perchlorate may lead to exposure in the developing fetus.
- Perchlorate exposure assessment in lactating women in San Diego. In collaboration with Dr. Phillip Alexander (University of California, San Diego) we are measuring perchlorate and iodine in breast milk and urine samples collected from women who drink tap water with perchlorate contamination below the California Public Health Goal level of 6 µg/L. Perchlorate levels in their drinking water will also be measured. This study will also examine the impact of a therapeutic dose of iodine on perchlorate clearance from the body.
- Perchlorate exposure assessment in lactating West Coast women. In collaboration with Kim Hooper (California EPA) we are measuring perchlorate in breast milk samples collected from nearly 250 women living in California and Washington. We plan to examine both the magnitude and variability in breast milk perchlorate levels. A dietary questionnaire is being used to identify potential sources of perchlorate from the diet.